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SYSTEMATIC REVIEW AND META-ANALYSIS

Drug-Coated Balloon Versus Plain Balloon Angioplasty for Hemodialysis Dysfunction: A Meta-Analysis of Randomized Controlled Trials

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BACKGROUND: Both drug-coated balloon (DCB) angioplasty and conventional plain balloon angioplasty (PBA) can be implemented to treat hemodialysis dysfunction. The present study aims to compare the safety and efficacy of these 2 approaches by conducting a meta-analysis of available randomized controlled trials.

METHODS AND RESULTS: PubMed, Cochrane Library, and Embase databases were queried from establishment to January 2021. A total of 18 randomized controlled trials including 877 and 875 patients in the DCB and PBA groups, respectively, were included in the present meta-analysis. Target lesion primary patency, circuit patency, target lesion revascularization, and mortality were pooled. Odds ratios (ORs) were reported with 95% CIs. Publication bias was analyzed with funnel plot and Egger test. Target lesion primary patency was higher among patients who underwent DCB (OR, 2.93 [95% CI, 2.13–4.03], $P<0.001$ at 6 months; OR, 2.47 [95% CI, 1.53–3.99], $P<0.001$ at 1 year). Also, the DCB group had a higher dialysis circuit patency at 6 months (OR, 2.42; 95% CI, 1.56–3.77 [$P<0.001$]) and 1 year (OR, 1.91; 95% CI, 1.22–3.00 [$P=0.005$]). Compared with the PBA group, the DCB group had lower odds of target lesion revascularization during follow-up (OR, 0.43 [95% CI, 0.23–0.82], $P=0.001$ at 6 months; OR, 0.74 [95% CI, 0.32–1.73], $P=0.490$ at 1 year). The OR of mortality was comparable between 2 groups at 6 months (OR, 1.18; 95% CI, 0.42–3.33 [$P=0.760$]) and 1 year (OR, 0.93; 95% CI, 0.58–1.48 [$P=0.750$]).

CONCLUSIONS: Based on evidence from 18 randomized controlled trials, DCB angioplasty is superior to PBA in maintaining target lesion primary patency and circuit patency among patients with dialysis circuit stenosis. DCB angioplasty also reduces target lesion revascularization with a similar risk of mortality compared with PBA.

Key Words: arteriovenous fistula ■ arteriovenous graft ■ balloon angioplasty ■ drug-coated balloon angioplasty ■ hemodialysis dysfunction ■ meta-analysis ■ plain balloon angioplasty

Approximately 1.2 million global annual deaths can be attributed to chronic kidney disease.[1] Hemodialysis via arteriovenous fistula (AVF) and arteriovenous graft (AVG) is a life-sustaining measure for patients with renal failure. However, vascular access dysfunction, mainly caused by stenosis, is the most frequent complication preventing hemodialysis and is associated with mortality and morbidity.[2–4] According to the Kidney Disease Outcomes Quality Initiative's clinical practice guideline, angioplasty can be implemented as the primary treatment for hemodialysis access stenosis.[5] While traditional plain balloon angioplasty (PBA) can expand the stenotic vessel lumen via mechanical dilation, drug-coated balloon (DCB) angioplasty has been proven effective in prolonging patency rate in patients with coronary artery

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CLINICAL PERSPECTIVE

What Is New?

- The present meta-analysis compared the safety and efficacy of drug-eluting balloon and plain balloon angioplasty in treating hemodialysis access dysfunction based on 18 randomized controlled trials.
- Drug-eluting balloon angioplasty is superior to plain balloon angioplasty during short-term follow-up regarding target lesion patency, circuit patency, and target lesion revascularization rates with a similar mortality profile.

What Are the Clinical Implications?

- Using drug-eluting balloon in treating hemodialysis access dysfunction may reduce the requirement of reintervention and its related healthcare cost compared with plain balloon angioplasty in the short-term.
- Existing clinical trials are encouraged to publish long-term results to compare the safety of drug-eluting balloon and plain balloon angioplasty.
- Future large and less heterogeneous randomized controlled trials are warranted.

Nonstandard Abbreviations and Acronyms

AVF	arteriovenous fistula
AVG	arteriovenous graft
DCB	drug-coated balloon
PBA	plain balloon angioplasty
TLPP	target lesion primary patency
TLR	target lesion revascularization

disease and peripheral artery disease (PAD), owing to the coating agent's inhibition of cell proliferation and reduced neointimal hyperplasia.[6,7]

In the past decade, the use of DCB has also gained popularity in the treatment of hemodialysis failure. However, despite promising results in retrospective comparative studies, randomized controlled trials (RCTs) comparing DCB and PBA have demonstrated conflicting results.[8,9] Based on a previous meta-analysis of RCTs by Liao et al in 2020, despite a trend favoring DCB over PBA, there was no statistically significant difference in efficacy as measured by patency rates between DCB and PBA, which might be attributed to underpowering.[10] Nonetheless, several new high-quality RCTs have been published since then.[9,11,12] The aim of the present study is to perform an updated meta-analysis of RCTs by expanding the sample size of data comparing the therapeutic efficacy and safety of DCB and PBA in treating hemodialysis access failure.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files. Because the present study is a systematic review and meta-analysis, institutional review board approval was not required.

Searching Strategy and Study Screening

MEDLINE, Embase, and Cochrane Library were queried from establishment to January 2021 without language restrictions. RCTs comparing DCB and PBA in hemodialysis were identified with keywords ("eluting" OR "coated") AND ("dialysis" OR "hemodialysis") AND ("random" OR "randomized") for PubMed, and "eluting," "coated," "dialysis," "randomized," and "balloon" for Cochrane.

The following inclusion criteria were adopted: (1) RCTs comparing DCB and PBA in treating patients with hemodialysis access failure; and (2) primary outcomes were reported: target lesion primary patency (TLPP), target lesion revascularization (TLR), circuit patency, and mortality. Exclusion criteria were as follows: (1) non-RCT (case report, case series, retrospective studies, nonrandomized prospective studies); (2) preclinical experiments of nonhuman subjects; (3) review, meta-analysis, editorial, commentary, or letter without original data; (4) studies containing patient samples used by more than 1 study; and (5) abstract or conference paper without full text. Endnote X8 (Clarivate Analytics) was implemented to identify duplicates and screen studies. Titles and abstracts were initially screened, followed by reviewing full texts of remaining studies (Figure 1).

Statistical Analysis

The following baseline set of information was extracted from each study: author, year of publication, region, sample size, race and ethnicity, age, number of AVF versus AVG, and length of follow-up. Quality assessment was performed using the Cochrane Collaboration's tool for RCTs (Table S1). Two researchers screened and extracted the data from the original studies. Any disagreement was discussed and resolved by consensus. Statistical analysis was performed with Stata 15.1 (STATA Corp.). Meta-analysis was conducted with the *-metan* function. TLPP, TLR, circuit patency, and mortality rates were analyzed with odds ratios (ORs) and 95% CIs. I^2 statistic was implemented to assess heterogeneity. A random-effects model was adopted to achieve a conservative estimate. Definitions of

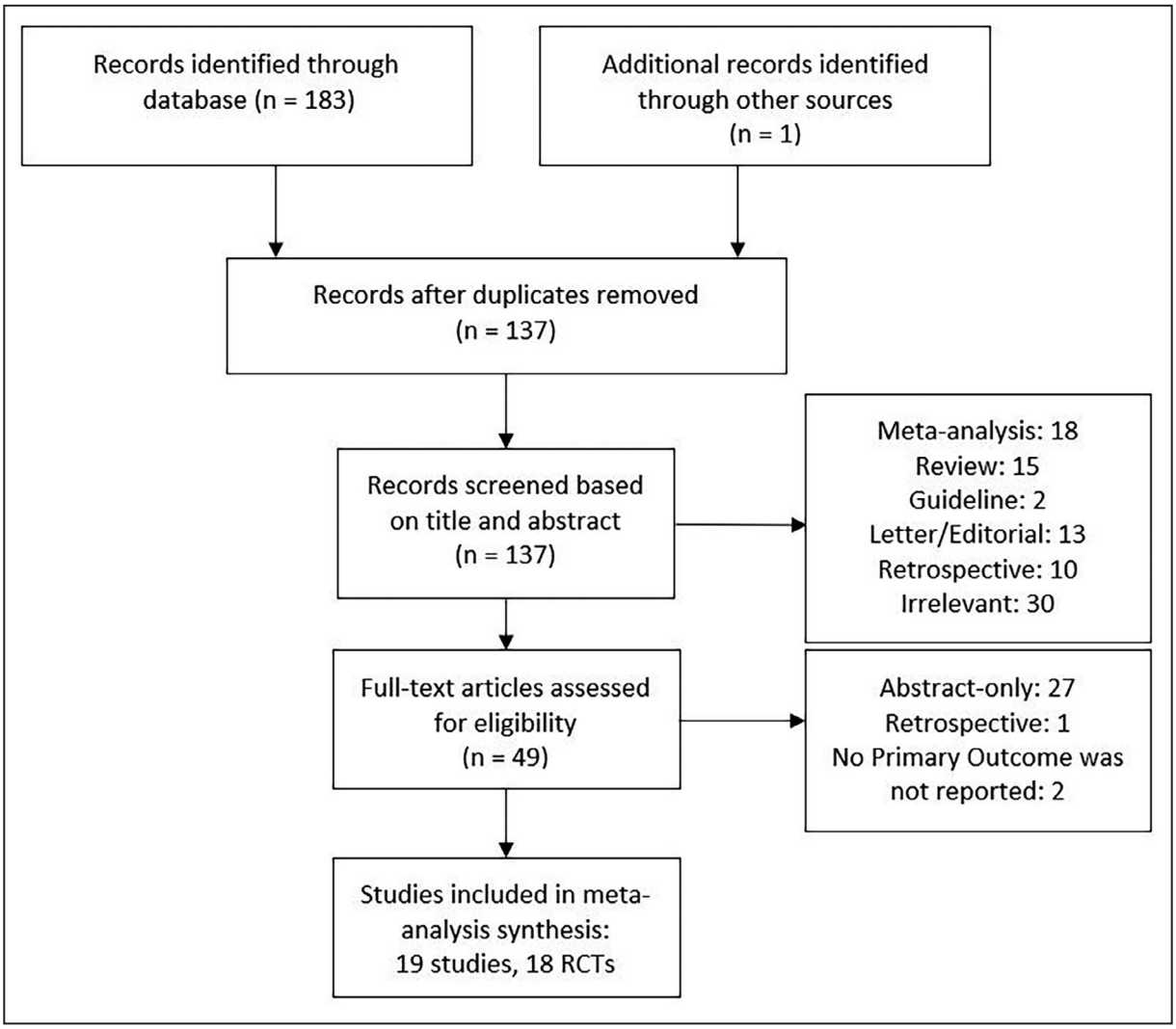

Figure 1. Flow diagram of the screening process.
RCT indicates randomized controlled trial.

TLPP, TLR, and circuit patency of each study were also extracted (Table S2). Forest plots were generated. Publication bias was evaluated with funnel plot and Egger test. Sensitivity analysis was performed using the *-metaninf* function (the 1-study removal approach).

RESULTS

Baseline Characteristics

A total of 137 studies were subjected to screening after removal of duplicates (Figure 1). Meta-analysis (n=18), reviews (n=15), letters or editorials (n=13), society guidelines (n=2), retrospective studies (n=10), and irrelevant studies (n=10) were removed. The resultant 49 studies were further screened by full-text assessment to remove publications without full text (n=27), retrospective studies (n=1), and studies without primary outcomes of interest reported (n=2), yielding 19 studies based on 18 unique RCTs.[8,11–28] A total of 877 and 875 patients in the DCB and PBA groups, respectively, were included in the present meta-analysis (Table 1). These studies were conducted in the United States, Korea, China, Egypt, Spain, Australia, Finland, Singapore, Belgium, Greece, Taiwan, the Netherlands, and Canada. Ten studies focused only on patients with AVF,* 1 study solely included patients with AVG,[21] and 7 studies enrolled patients with both AVF and AVG. Patency of dialysis access was evaluated by Doppler ultrasounds, fistulogram, and physical examination. The commercial brands of balloons and their respective paclitaxel doses are listed in Table 1.

Target Lesion Primary Patency

TLPP was reported by 12 studies at 6 months (Figure 2). A total of 493 of 659 (74.8%) and 364 of 682 (53.4%)

*References 8,9,11,14,16,17,20,22,26,28,29.

Table 1. Baseline Characteristics of Included Studies

Study	Region	Age, y, mean±SD	Patients, n	AVF/AVG	Patency evaluation method	Type/brand of balloon (coated vs standard)
Yin 2021[28]	China	DCB: 56±13 PBA: 54±13	DCB: 78 PBA: 83 Total: 161	AVF only	Doppler ultrasound	Coated: APERTO (3.0 μg/mm^2) Plain: OHICHO II HPBs (Kaneka Corporation; RBP 20–22 atm)
Lookstein 2020[11]	Multiple	DCB: 65.8±13.1 PBA: 65.5±13.4	DCB: 170 PBA: 160 Total: 330	AVF only	Duplex ultrasound	Coated: IN.PACT (Medtronic) (3.5 μg/mm^2) Plain: (non–drug-coated) balloon
Kim 2020[16]	Korea	DCB: 60.7±12.2 PBA: 63.7±11.8	DCB: 20 PBA: 19 Total: 39	AVF only	Angiogram	Coated: IN.PACT Admiral, Medtronic Plain: Mustang
Pang 2020[24]	China	DCB: 58.1±8.93 PBA: 57.4±6.9	DCB: 20 PBA: 20 Total: 40	AVF: 28 AVG: 12	Duplex ultrasound	Coated: IN.PACT Admiral (3.0 μg/mm^2) Plain: Medtronic Admiral balloon (semicompliant)
Karmota 2020[14]	Egypt	DCB: 54.7±13.2 PBA: 49.2±11.5	DCB: 30 PBA: 30 Total: 60	AVF only	Duplex ultrasound	Coated: Lutonix 035, Bard Peripheral Vascular Plain: unspecify
Moreno-Sánchez 2020[23]	Spain	67.4±12.6	DCB: 70 PBA: 78 Total: 148	AVF: 136 AVG: 12	Doppler Ultrasound and/or angiography	All initially treated with heparin (HPB) (Passeo 35 HP(R), Biotronik SE & Co. KG) Coated: Passeo-18 Lux(R) with BTHC hydrophobic excipient (Biotronik SE & Co. KG, Berlin, Germany) Plain: unspecified
Trerotola 2020[27]	United States	N/A	DCB: 141 PBA: 144 Total: 285	AVF only	Clinical	Drug: 2 μg/mm^2 of paclitaxel (total dose, 0.5–3.77 mg depending on balloon) Plain: control balloon of similar design but without drug coating
Liao 2020[10]	China	DCB: 70.4±10.6 PBA: 65.9±15.9	DCB: 22 PBA: 22 Total: 44	AVG only	Angiogram and transonic examination	Coated: IN.PACT Admiral DEB (Medtronic) Plain: Wanda (Boston Scientific), Mustang (Boston Scientific), and Armada (Abbott)
Swinnen 2019[26]	Australia	DCB: 65.2±13.6 PBA: 64.5±13.9	DCB: 70 PBA: 62 Total: 132	AVF only	Ultrasound	Coated: IN.PACT Admiral/Pacific (Medtronic) (3 μg/mm^2) Plain: uncoated angioplasty balloon of the operator's choice
Björkman 2019[8]	Finland	67.2	DCB: 18 PBA: 18 Total: 36	AVF only	Ultrasound	Coated: IN.PACT, Medtronic) (3.5 μg/mm^2 with urea as excipient) Plain: unspecified
Irani 2018[13]	Singapore	59.2 (range, 25–83)	DCB: 59 PBA: 60 Total: 119	AVF: 98 AVG: 21	Angiogram	Coated: IN PACT Admiral DEB (Invatec/Medtronic) (3 μg/mm^2 with irea as excipient) Plain: conventional balloon
Maleux 2017[22]	Belgium	DCB: 69.3±14.9 PBA: 66.9±17.0	DCB: 33 PBA: 31 Total: 64	AVF only	Physical examination	Coated: IN.PACT Admiral; Invatec/Medtronic) Plain: Admiral Extreme; Invatec/Medtronic)
Kitrou 2017[18]	Greece	DCB: 56.7 PBA: 57	DCB: 20 PBA: 20 Total: 40	AVF: 19 AVG: 21	Angiogram	Coated: IN.PACT (Invatec/Medtronic) (2 μg/mm^2) Plain: conventional balloon angioplasty
Kitrou 2015/ Katsanos 2012[15,17]	Greece	DCB: 65.7±13.2 PBA: 62.5±15.4	DCB: 20 PBA: 20 Total: 40	AVF: 14 AVG: 26	Angiogram	Coated: IN.PACT (Invatec/Medtronic) (3 μg/mm^2) Plain: conventional balloon angioplasty
Kitrou 2015[19]	Greece	61±14.6	DCB: 20 PBA: 20 Total: 40	AVF only	Angiogram	Coated: IN.PACT (Invatec/Medtronic) (2 μg/mm^2) Plain: high-pressure balloon
Lai 2014[20]	Taiwan	67.2±9.4	DCB: 10 PBA: 10 Total: 20	AVF only	Angiogram	Coated: Foxplus/Abott; Invatec/Medtronic) dose unspecified Plain: unspecified
Roosen 2017[25]	Netherlands	DCB: 80 (range, 71–86) PBA: 83 (range, 78–86)	DCB: 16 PBA: 18 Total: 34	AVF: 29 AVG: 5	Duplex ultrasound	Coated: Invatec/Medtronic, dose unspecified Plain: conventional balloon angioplasty (Sterling/Boston Scientific)
Therasse 2020[9]	Canada	DCB: 63.5±12.6 PBA: 66.6±12.6	DCB: 60 PBA: 60 Total: 120	AVF: 109 AVG: 11	Angiogram	Coated: Passeo-18 Lux/Biotronik, dose unspecified Plain: same type/brand without drug

AVF indicates arteriovenous fistula; AVG, arteriovenous graft; DCB, drug-coated balloon; N/A, not available; PBA, plain balloon angioplasty; and RBP, rated burst pressure.

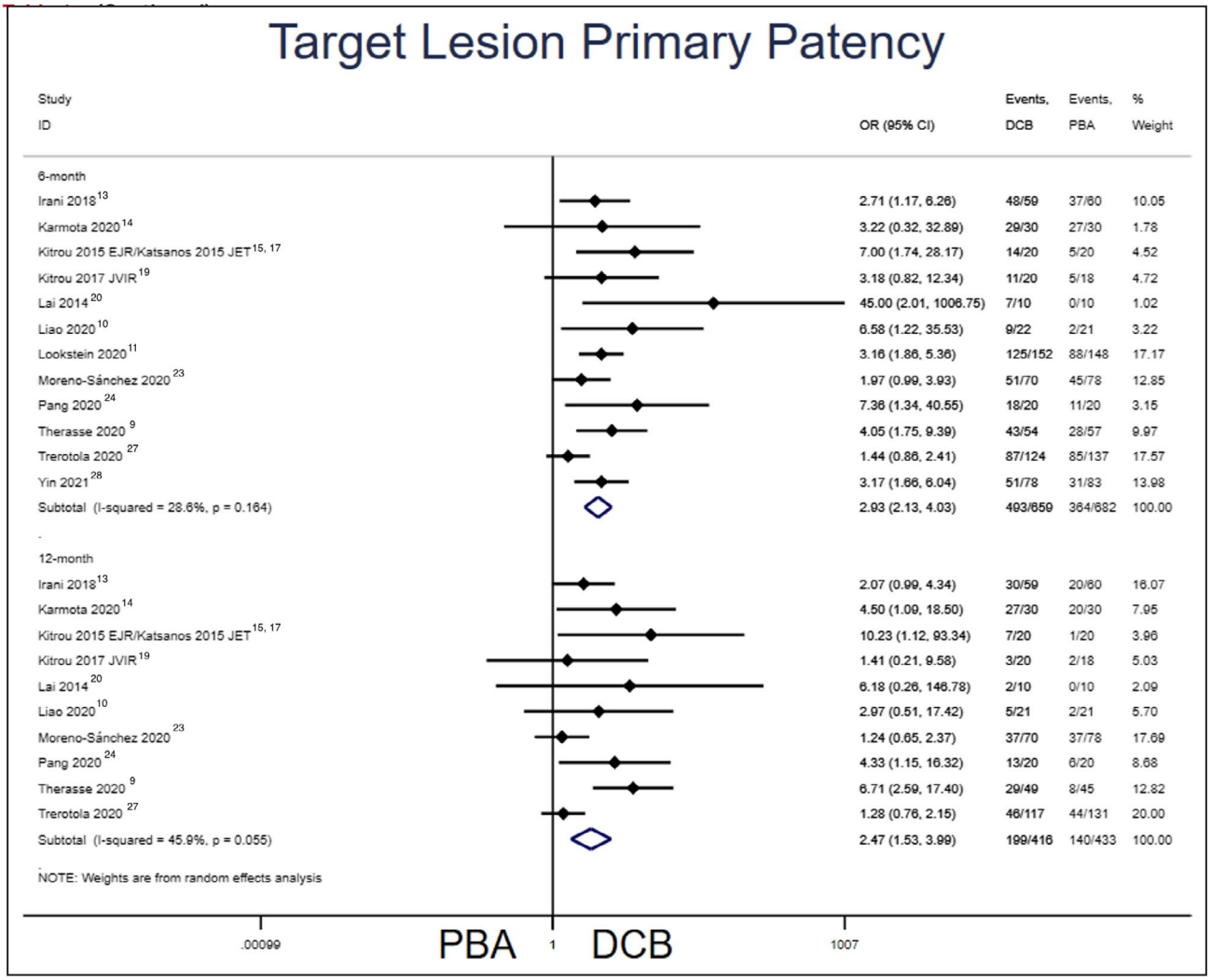

Figure 2. Target lesion primary patency after drug-coated balloon (DCB) angioplasty and plain balloon angioplasty (PBA). Odds ratios (ORs) with 95% CIs were stratified by follow-up length (6 and 12 months).

lesions by DCB and PCA were patent, respectively, with an OR of 2.93 (95% CI, 2.13–4.03; *P*<0.001 [I^2=28.6%]). Based on 10 studies at 12 months, the patency rate in DCB and PCA groups were 199 of 416 (47.8%) and 140 of 433 (32.3%), respectively. The OR was 2.47 (95% CI, 1.53–3.99; *P*<0.001 [I^2=45.9%]). Funnel plots (Figure S1) suggested possible publication bias at 6 months (Egger test *P*=0.012) and 12 months (Egger test *P*=0.039). For patients with AVF, the TLPP rates were 338 of 439 (77.0%) versus 258 of 458 (56.3%) at 6 months (OR, 2.94; 95% CI, 1.77–4.89 [*P*<0.001]; I^2=52.7%) and 152 of 290 (52.4%) versus 116 of 308 (37.7%) at 12 months (OR, 2.40; 95% CI, 1.27–4.53 [*P*=0.007]; I^2=59.2%) for the DCB and PBA groups, respectively (Table S3).

Dialysis Circuit Patency Rate

Dialysis circuit patency rate at 6 months was reported by 9 studies including 510 and 518 patients treated with DCB and PBA, respectively (Figure 3). The rate of circuit patency was 359of 510 (70.4%) in DCB and 274 of 518 (52.9%) in PBA groups (OR, 2.42; 95% CI, 1.56–3.77 [*P*<0.001]; I^2=48.8%). Seven studies reported circuit patency at 12 months. A total of 137 of 318 (43.1%) and 100 of 322 (31.1%) patients had patent dialysis circuits, with an OR of 1.91 (95% CI, 1.22–3.00; *P*=0.005 [I^2=16.1%]). Funnel plots did not suggest publication bias (Figure S1; Egger test *P*=0.386 at 6 months and *P*=0.535 at 12 months). For the AVF subgroup, the circuit patency rates were 288 of 428 (67.3%) versus 228 of 435 (52.4%) at 6 months (OR, 1.84; 95% CI, 1.13–2.99 [*P*=0.014]; I^2=50.9%) and 111 of 259 (42.9%) versus 90 of 264 (34.1%) (OR, 1.56; 95% CI, 1.04–2.35 [*P*=0.032]; I^2<0.1%) at 12 months for DCB and PBA groups, respectively (Table S3).

TLR Rate

Based on 9 studies, the TLR rate was 109 of 410 (26.6%) in patients with DCB and 175 of 395 (44.3%) in patients with PBA at 6 months (Figure 4). The OR

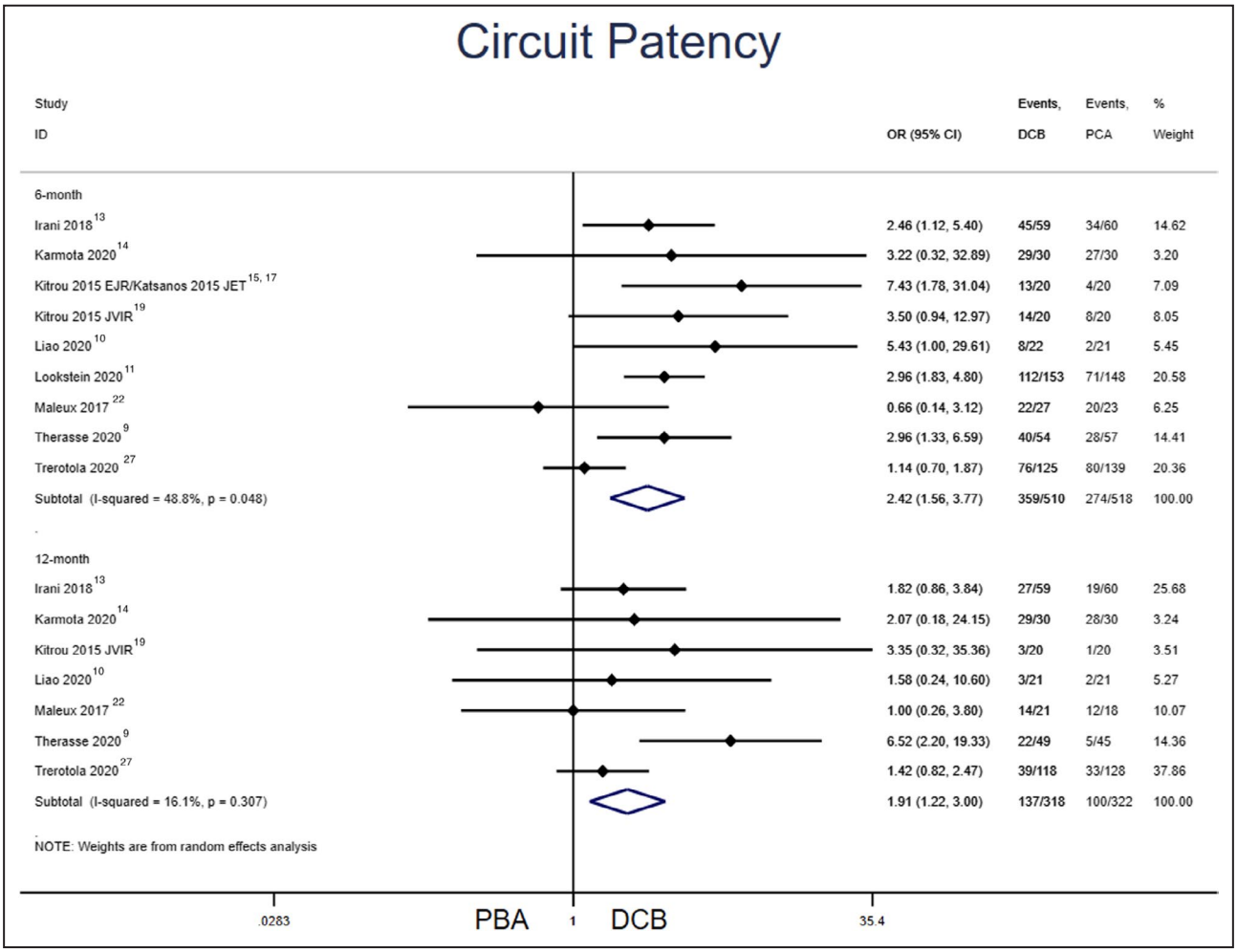

Figure 3. Circuit patency after drug-coated balloon (DCB) angioplasty and plain balloon angioplasty (PBA).
Odds ratios (ORs) with 95% CIs were stratified by follow-up length (6 and 12 months).

was 0.43 (95% CI, 0.23–0.82; P=0.001 [I^2=65.4%]). Based on 8 studies at 12 months, the DCB group had a TLR rate of 138 of 248 (55.6%), while PBA had a TLR rate of 152 of 245 (62.0%). The OR was 0.74 (95% CI, 0.32–1.73; P=0.4900 [I^2=67.1%]). Funnel plot showed symmetrical distribution (Figure S1; Egger test P=0.521 at 6 months and P=0.694 at 12 months). Based on sensitivity analysis, the lack of statistical significance at 12-month follow-up seemed to be the sequela of including the study by Bjorkman et al, which draws contradictory conclusions compared with all other studies (Figure S2A). The removal of this outlier restored the overall statistical significance, demonstrating a lower TLR rate among patients treated with DCB (OR, 0.53; 95% CI, 0.35–0.82 [P=0.004]; I^2<0.1%) (Figure S2B). In addition to the decrease in heterogeneity from 67.1% to <0.1%, the P value of heterogeneity also increased from 0.003 to 0.64. For patients with AVF, the TLR rate was 86 of 352 (24.4%) versus 133 of 339 (39.2%) (OR, 0.61; 95% CI, 0.27–1.37 [P=0.232]; I^2=74.5%) at 6 months and 94 of 191 (49.2%) versus 100 of 189 (52.9%) at 12 months (OR, 1.05; 95% CI, 0.37–3.00 [P=0.922]; I^2=77.4%) for the DCB and PBA groups, respectively (Table S3). After the study by Bjorkman et al was removed (Figure S3), the TLR rate became 73 of 334 versus 128 of 321 at 6 months (OR, 0.38; 95% CI, 0.24–0.59 [P<0.001]; I^2=21.2%) and 78 of 173 (42.5%) versus 96 of 171 (55.2%) (OR, 0.58; 95% CI, 0.36–0.91 [P=0.019]; I^2<0.1%).

Mortality Rate

Mortality was reported by 7 studies at 6 months and 12 studies at 1 year (Figure 5). At 6 months, the mortality rates were 17 of 324 (5.2%) and 14 of 309 (4.5%) among patients who underwent DCB and PBA, respectively. The OR was comparable at 1.18 (95% CI, 0.42–3.33; P=0.760 [I^2=35.7%]). Based on 12 studies at 12 months, the mortality rates were 38 of 563 (6.75%) and 41 of 563 (7.28%) in the DCB and PBA groups, respectively, with an OR of 0.93 (95% CI, 0.58–1.48;

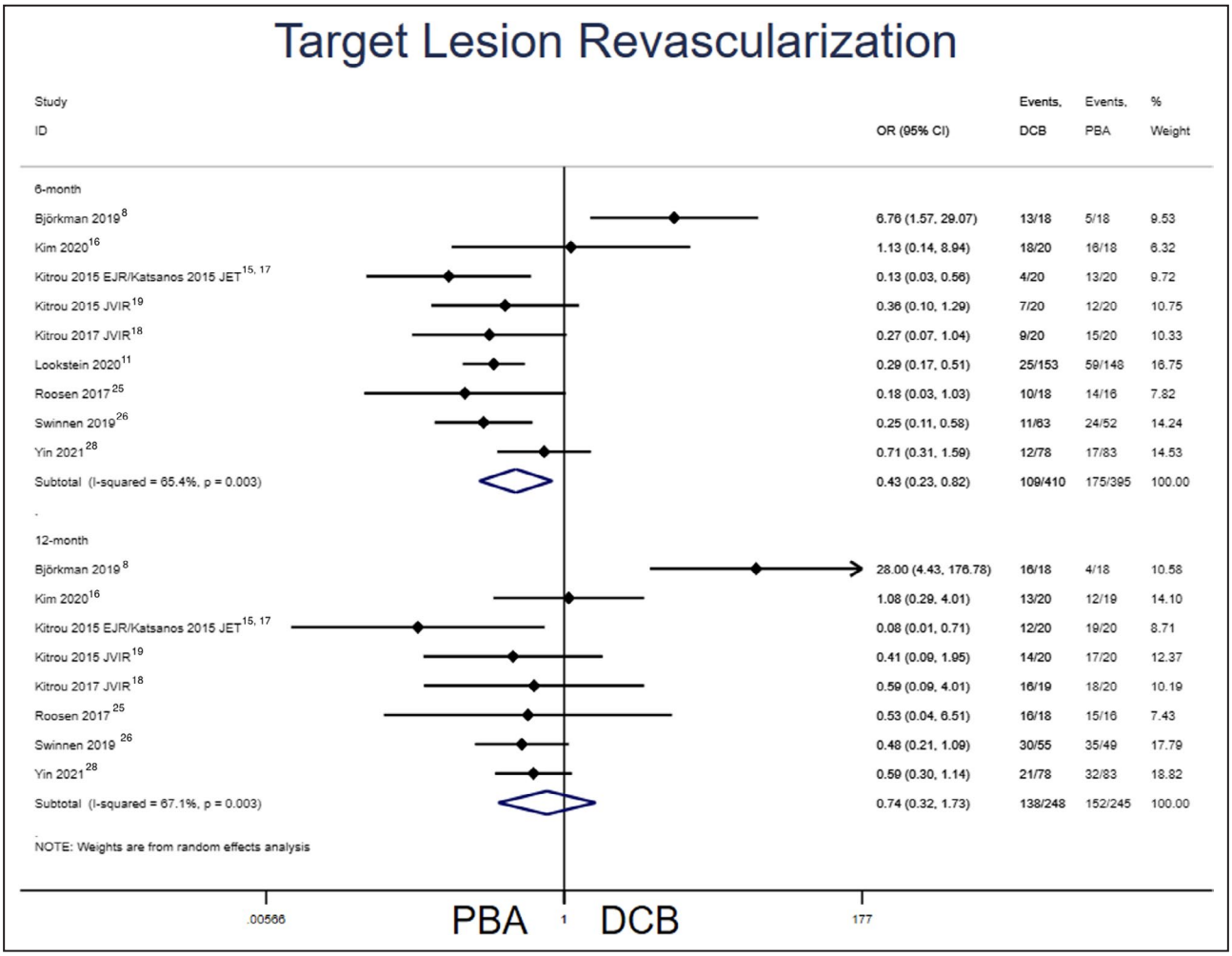

Figure 4. Target lesion revascularization after drug-coated balloon (DCB) angioplasty and plain balloon angioplasty (PBA). Odds ratios (ORs) with 95% CIs were stratified by follow-up length (6 and 12 months).

P=0.750 [I^2<0.1%]). Funnel plots suggested low risk of publication bias (Figure S1; Egger test *P*=0.064 at 6 months and *P*=0.727 at 12 months). Among patients with AVF, the mortality rates were 12 of 254 (4.7%) versus 10 of 239 (4.2%) at 6 months (OR, 0.95; 95% CI, 0.18–4.95 [*P*=0.950]; I^2=54.7%) and 23 of 327 (7.0%) versus 26 of 318 (8.2%) at 12 months (OR, 0.87; 95% CI, 0.48–1.59 [*P*=0.650]; I^2<0.1%) for the DCB and PBA cohorts, respectively (Table S3).

Complications

Six studies reported procedure-related adverse effects (Table S3). The cumulative incidence of complication was 2.30% in DCB versus 4.35% in PBA (Table 2). The incidence of each category of complication was <0.8%, except for the hematoma rate in PBA (2%). The following complications were pooled: vasospasm (0.77% versus 0.51%), hematoma (0.26% versus 2.05%), dissection (0.51% versus 0.77%), vein break (0.26% versus 0.77%), pseudoaneurysm (0.26% versus 0%), drug allergy (0.26% versus 0%), and thrombosis arterial embolism (0% versus 0.26%) between DCB and PBA, respectively. The drug allergy that occurred in 1 patient with DCB was caused by an allergic reaction to the contrast agent rather than paclitaxel, which subsequently induced a thrombosis event that occluded the cephalic vein.

Outcomes Beyond 1-Year Follow-Up

Few studies have reported outcomes beyond a 1-year follow-up (Figure S4). TLPP was analyzed by 3 studies at 18-month (DCB versus PBA: 43 of 146 [29.5%] versus 42 of 166 [25.3%], *P*=0.496) and 2 studies at 24-month follow-up (9 of 104 [8.7%] versus 10 of 119 [8.4%], *P*=0.634), respectively. Based on the 3 studies at 18-month follow-up, 55 of 56 (98.2%) and 54 of 56 (96.4%) patients with DCB and PBA required TLR at 18 months (*P*=0.683), while 36 of 36 (100%) and 37

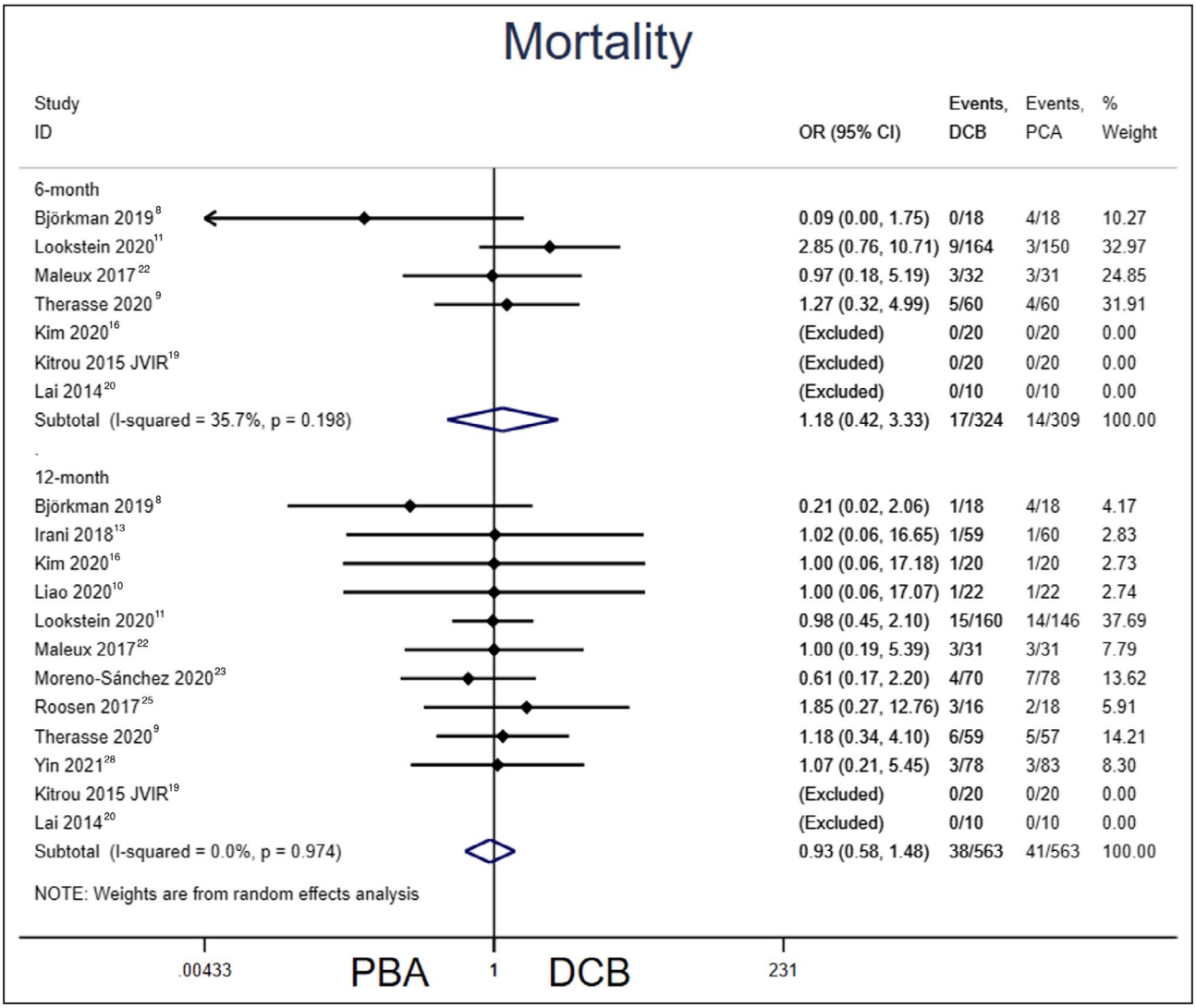

Figure 5. Mortality after drug-coated balloon (DCB) angioplasty and plain balloon angioplasty (PBA).
Odds ratios (ORs) with 95% CIs were stratified by follow-up length (6 and 12 months).

of 38 (97.4%) underwent TLR at 24-month follow-up (*P*=0.490). Two studies reported circuit patency rates at 18-month follow-up with a pooled rate of 24 of 133 (18.0%) and 25 of 150 (16.7%) for the DCB and PBA groups, respectively (*P*=0.689). According to 1 study, no patient maintained circuit patency at 24-month follow-up in either group. Based on 2 studies, the 2-year mortality rates of DCB and PBA groups were 46 of 198 (23.2%) and 37 of 200 (18.5%) (*P*=0.367), respectively.

DISCUSSION

Based on data from 1752 patients included in the 18 RCTs selected, DCB is more effective than PBA in preventing hemodialysis access failure after endovascular recanalization. Overall, the DCB group demonstrated more favorable TLPP, TLR, and circulation patency rates (Figures 2 through 4). This observation aligns with previous evidence on the superior efficacy of DCB over conventional balloons in treating PAD and coronary artery disease.[30] In these settings, arterial stenosis resulted from vascular remodeling and neointimal hyperplasia mediated by inflammation and smooth muscle proliferation. Paclitaxel, a commonly used chemotherapy agent for drug-coated balloons, inhibits smooth muscle cell proliferation and thus reduces the risk of restenosis following angioplasty.[31,32] By contrast, in hemodialysis access, a variety of factors including altered postsurgical flow dynamics, shear wall stress from dialysis, and venous arterialization renders venous outflow as the accountable culprit for intimal proliferation and stenosis.[33,34] While PBA intervention could exacerbate this process by damaging the vessel wall through dilatation, paclitaxel, coated on the DCB surface, partitions through the vessel wall, which, in turn, inhibits cellular proliferation and prevents restenosis.[35]

Table 2. Pooled Incidence of Complications

Complication type	DCB, n (%)	PBA, n(%)
Vasospasm	3 of 392 (0.77)	2 of 391 (0.51)
Hematoma	1 of 392 (0.26)	8 of 391 (2.05)
Dissection	2 of 392 (0.51)	3 of 391 (0.77)
Vein break	1 of 392 (0.26)	3 of 391 (0.77)
Pseudoaneurysm	1 of 392 (0.26)	0 of 391 (0.00)
Drug allergy	1 of 392 (0.26)	0 of 391 (0.00)
TAE	0 of 392 (0.00)	1 of 391 (0.26)
Total	9 of 392 (2.30)	17 of 391 (4.35)

DCB indicates drug-coated balloon angioplasty; PBA, plain balloon angioplasty; and TAE, thrombosis arterial embolism.

In addition to the primary end points previously mentioned, the efficacy of angioplasty should be evaluated by the number of angioplasties required to maintain patency, as repeated angioplasty results in higher overall cost. In the study performed by Lookstein et al, the average number of interventions required to maintain access-circuit primary patency was significantly lower in patients treated with DCB compared with those treated with PBA (0.3 versus 0.6 reintervention per person, respectively; $P<0.001$).[11] Similar results were observed in the study by Katsanos et al (reintervention rate: 20% versus 65%, $P=0.002$).[15] According to Trerotola et al, respectively, the DCB group required significantly fewer intervention than its PBA counterpart at 3 months (11 versus 19, $P=0.048$), 6 months (44 versus 64, $P=0.034$), and 9 months (75 versus 102, $P=0.021$).[29] Although the present meta-analysis did not shed light on the difference in cost between DCB and repeated angioplasty using PBA, the pooled results of TLPP, TLR, and circulation patency rates could serve as a reference for future cost-effectiveness study designs.

Although 18 RCTs have been published, mid-term and long-term RCT results beyond 1-year follow-up remain scarce. Trerotola et al observed TLLP rates of 27% versus 24% ($P=0.09$) between DCB and PBA groups, respectively, at 2 years,[29] whereas Kim et al reported rates of 55.0% and 57.0%, respectively ($P=0.90$).[16] Only 1 to 3 studies from the present meta-analysis reported a clinical outcome of interest beyond 1-year follow-up (Figure S4). Because of underpowering, no statistically significant difference was observed between the 2 treatment groups regarding TLPP, TLR, circuit patency, and mortality rates. Critical analysis of outcomes beyond 1-year follow-up was deferred in the present meta-analysis because of the paucity of data, although such information may aid power calculations for future large RCTs. Based on nonrandomized comparative studies, pooled results from prior meta-analyses suggested a higher TLPP among patients with dialysis failure treated with DCB ($P=0.009$) at 24-month follow-up,[36] although the inherent selection bias in study design must be accounted for. Whether DCB can provide a durable long-term patency rate over PBA remains to be determined by large RCTs.

From a safety standpoint, both interventions exhibited similar immediate complication rates (Table 2). The difference of the rates of each complication category was <2% between the 2 groups, which is clinically insignificant. The mortality rate between patients who received DCB and PBA were also comparable at 6-month and 1-year follow-up (Figure 5). By contrast, a previously published meta-analysis of RCTs on femoral PAD raised the concern that paclitaxel-coated balloons and stents were associated with a higher mortality rate,[37] although the exact mechanism remained unknown. Moreover, the previously published meta-analysis study design was subject to fierce debate. The risk of deaths among patients with PAD treated with DCB did not manifest until 2-year follow-up, whereas results from our study were limited to short-term (<1 year). Unlike patients with PAD, patients with renal failure requiring dialysis are more likely to succumb to the nature of the disease, rendering long-term follow-up data difficult. Based on the study by Trerotola et al, the 2-year mortality rates were comparable between the 2 groups (DCB versus PBA: 23% versus 18%, $P=0.27$).[29] According to a previous meta-analysis including retrospective evidence, no significant difference in mortality was observed between the 2 groups at 2-year follow-up.[36] Publishing long-term survival results from the existing RCTs included in the present meta-analysis can be fundamental in determining the relationship between paclitaxel-coated balloons and mortality among patients with hemodialysis failure.

Notably, sirolimus DCB and stents have recently gained popularity because of the concern of paclitaxel-related mortality among patients with PAD.[38,39] Its reported use in hemodialysis failure was limited to noncomparative studies. Tan et al performed sirolimus DCB angioplasty in 20 patients, achieving a 6-month primary circuit patency rate of 65%, with a mean patency rate of 285 days (95% CI, 194–376 days).[12] Although no study has compared sirolimus with paclitaxel DCB in the use of hemodialysis access in patients, evidence from coronary artery interventions has demonstrated comparable efficacy of sirolimus- and paclitaxel-coated stents and balloons.[40,41] As such, future comparative studies are warranted to evaluate their use in patients with hemodialysis access failure, if DCB is truly deleterious to patients with hemodialysis failure.

The results of the present meta-analysis should be interpreted with caution. First, the measurement of stenosis varied among institutions. In addition to the percentage of stenosis, a variety of measuring methods were adopted: ultrasound, angiogram, clinical examination, or a combination of these.

Nomenclature-wise, it is crucial for professional society guidelines to unify the definition of clinical outcomes. For example, TLPP refers to anatomical stenosis below a certain threshold, as well as the lack of requiring revascularization at target lesions, whereas other studies consider only the anatomical aspects. Establishing standard outcome-reporting guidelines may promote the critical analysis among published evidence in the future. Furthermore, the patient population included in the investigation may differ among individual studies. For instance, although overall TLR appears to be the same between DCB and PBA groups, the exclusion of Bjorkman et al rendered the results statistically significant, favoring DCB. The unique findings observed in Bjorkman et al's study was hypothesized to be attributed to the enrollment of immature hemodialysis access <1 year old.[10,42] Because of the heterogeneity of each individual study's baseline characteristics and variances in clinical outcome definitions, a random model was adopted in the present meta-analysis to achieve a more conservative estimate. Moreover, the present study included patients with both AVF and AVG. Although subgroup analysis of AVF-only studies suggested a favorable performance of DCB over PBA, a meta-analysis of the AVG group was not performed as Liao et al was the only study that demonstrated higher TLPP (23% versus 9%) and circuit patency (14% versus 9%) rates in the DCB group.[21] Thus, the results of this present meta-analysis might be more applicable to AVF failures. Additionally, stratification based on balloon type and drug-coating dose was not performed. In theory, a higher paclitaxel dose may be more effective in preventing restenosis; however, this approach is further complicated by the characteristics of the stenosis burden. For multiple lesions and patients with longer segments of occlusion, a higher dose of paclitaxel might be delivered during angioplasty. As such, the true dose of coated paclitaxel that each patient received is uncertain. Finally, the present meta-analysis did not consider RCTs with preliminary results presented during conferences and unpublished in peer-reviewed journals as full and complete articles. The exclusion of these RCTs may undermine the power of the present meta-analysis.

CONCLUSIONS

Based on evidence from the RCTs explored in this present study, it is evident that DCB offers a significantly more favorable short-term outcome for patients with hemodialysis access failure in terms of TLPP, circuit patency, and TLR rates. Furthermore, similar mortality rates were observed between patients treated with DCB and PBA. Future large-scale multicenter RCTs with long-term follow-up data are warranted.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S3
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Quality Assessment.

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Yin 2021[28]	+	+	+	+	+	+	+
Lookstein 2020[11]	+	-	+	-	+	+	+
Kim 2020[16]	+	-	+	-	+	+	+
Pang 2020[24]	+	+	+	+	+	+	+
Karmota 2020[14]	-	?	+	?	+	+	+
Moreno-Sánchez 2020[23]	+	?	+	?	+	+	+
Trerotola 2020[27]	+	+	+	+	+	+	+
Liao 2020[10]	+	+	+	+	+	+	+
Swinnen 2019[26]	+	+	+	+	+	+	+
Björkman 2019[8]	+	+	+	+	+	+	+
Irani 2018[13]	+	-	-	-	+	+	+
Maleux 2017[22]	+	-	-	+	+	+	+
Kitrou 2017 JVIR[18]	+	-	+	+	+	+	+
Kitrou 2015 EJR/Katsanos 2015 JET[15, 17]	+	-	+	-	+	+	+
Kitrou 2015 JVIR[19]	+	-	-	-	+	+	+
Lai 2014[20]	-	?	?	?	+	+	+
Roosen 2017[25]	+	-	+	-	+	+	+
Therasse 2020[9]	+	-	+	-	+	+	+

Table S2. Dialysis access patency surveillance methods and definitions of clinical outcomes of each individual study.

Study	Patency evaluation method	Target Lesion Patency	Target Lesion Revascularization	Circuit patency
Yin 2021[28]	Doppler ultrasound at regular intervals. Clinically otherwise.	Doppler peak systolic velocity ratio ≤2.0 at target lesion without intervention.	Any reintervention in the target lesion (+/- 5 mm proximal or distal to the target lesion determined by ultrasound due to clinical indicators with potential stenosis	The lack of any reintervention in the shunt determined by ultrasound due to clinical indicators with potential stenosis
Lookstein 2020[11]	Duplex ultrasound at regular intervals. Clinically and angiogram as needed otherwise.	Freedom from clinically driven target-lesion revascularization or access-circuit thrombosis measured during the 6 months after the index procedure	Target-lesion revascularization if the target lesion either had stenosis of at least 50% of the diameter of the vessel (per angiographic core laboratory assessment) in the presence of clinical or physiological abnormalities that indicated dialysis access dysfunction or had at least 70% stenosis in the absence of abnormalities that indicated dysfunction	Access-circuit thrombosis
Kim 2020[16]	Clinical, ultrasound, angiogram	NA	Functional dialysis circuit with no clinical need for repeat intervention at the target lesion.	NA
Pang 2020[24]	Duplex ultrasound at regular intervals. Clinical, angiogram.	Functional dialysis access with <50% restenosis and without any repeat interventional procedures at target lesions	NA	NA
Karmota 2020[14]	Clinical, ultrasound, angiogram	Lack of significant binary re-stenosis greater than 50% needing further intervention at the target lesion or within 5mm distal or proximal to target lesion	NA	Significant binary re-stenosis greater than 50% needing further intervention at the target lesion or within 5mm distal or proximal to target lesion
Moreno-Sánchez 2020[23]	Clinical, angiogram	Stenosis < 50% or vein diameter > 2 mm at target lesions without clinical failure.	NA	NA
Trerotola 2020[27]	Clinical, angiogram	Society of Interventional Radiology Guideline	NA	Society of Interventional Radiology Guideline
Liao 2020[10]	Clinical, ultrasound, angiogram	<50% restenosis without correlated clinical evidence of graft dysfunction requiring re-intervention (ie, abnormal physical examination findings suggesting vascular access dysfunction; reduction in flow rate of >25% from baseline or total access blood flow rate of <600 mL/min by transonic examination; and increased dynamic venous pressure during dialysis exceeding the threshold level on three consecutive measurements.	NA	No need for intervention of the entire dialysis access
Swinnen 2019[26]	Scheduled ultrasound. Clinically driven otherwise.	NA	Absence of any repeat intervention in the target lesion during the follow-up period	NA

Björkman 2019[8]	Ultrasound at scheduled intervals. Clinically driven otherwise.	NA	Revascularization due to the same lesions	NA
Irani 2018[13]	Scheduled angiogram	<50% stenosis and absence of any repeat intervention in the target lesion	NA	No need of access intervention anywhere in the dialysis circuit
Maleux 2017[22]	Clinical	NA	NA	A patent fistula allowing continued successful and efficient dialysis sessions without the need for repeat endovascular and/or surgical revision
Kitrou 2017 JVIR[18]	Clinically driven , angiogram	< 30% residual diameter stenosis by visual estimation or decrease of collateral vessels	Functional dialysis circuit with no need for clinically driven target lesion repeat intervention	Patent circuit allowing adequate dialysis without any additional revascularization procedures at any site within the circuit.
Kitrou 2015 EJR/Katsanos 2015 JET[15, 17]	Clinically driven, angiogram	<50% angiographic restenosis with no need for any additional percutaneous or surgical procedure within the previously treated area.	Lack of re-intervention (surgical or percutaneous) due to restenosis	dialysis access thrombosis
Kitrou 2015 JVIR[19]	Clinically driven, angiogram	NA	A functional dialysis circuit with no need for clinically driven target lesion repeat intervention	A patent circuit allowing adequate dialysis without any additional revascularization procedures at any site within the circuit
Lai 2014[20]	Clinical, Angiogram	Target lesion with a lumen reduction of < 50% without the need of another percutaneous intervention for a lumen reduction>50%	.NA	NA
Roosen 2017[25]	Scheduled ultrasound	NA	Revascularization due to target lesion	NA
Therasse 2020[9]	Clinical, scheduled angiogram	<50% restenosis along target lesions	NA	The lack of thrombosis, reintervention including creation of a new dialysis access, or placement of dialysis catheter

NA: not available.

Table S3. **Subgroup analysis of patients with arteriovenous fistula.**

Variables	Rate	Odds Ratio	95% Confidence Interval	P value	Heterogeneity
Target Lesion Primary Patency					
6-month	DCB: 338/439 (77.0%) PBA: 258/458 (56.3%)	2.942	(1.77-4.89)	<0.001	0.527
12-month	DCB: 152/290 (52.4%) PBA: 116/308 (37.7%)	2.40	(1.27, 4.53)	0.007	0.592
Target Lesion Revascularization					
6-month	DCB: 86/352 (24.4%) PBA: 133/339 (39.2%)	0.61	(0.27-1.37)	0.232	0.745
12-month	DCB: 94/191 (49.2%) PBA 100/189 (52.9%)	1.05	(0.37, 3.00)	0.922	0.774
Circuit Patency					
6-month	DCB: 288/438 (67.3%) PBA: 228/435 (52.4%)	1.84	(1.13, 2.99)	0.014	0.509
12-month	DCB: 111/259 (42.9%) PBA 90/264 (34.1%)	1.56	(1.04, 2.35)	0.032	0
Mortality					
6-month	DCB: 12/254 (4.7%) PBA: 10/239 (4.2%)	0.95	(0.18, 4.95)	0.95	0.574
12-month	DCB: 23/327 (7.0%) PBA 26/318 (8.2%)	0.87	(0.48-1.59)	0.65	0

DCB: drug-coated balloon angioplasty. PBA: plain-balloon angioplasty.

Figure S1. **Funnel plots.** Targe Lesion Primary Patency (A: 6-month, B: 12-month). Target Lesion Revascularization (A: 6-month, B: 12-month). Circuit Patency (A: 6-month, B: 12-month). Mortality (A: 6-month, B: 12-month).

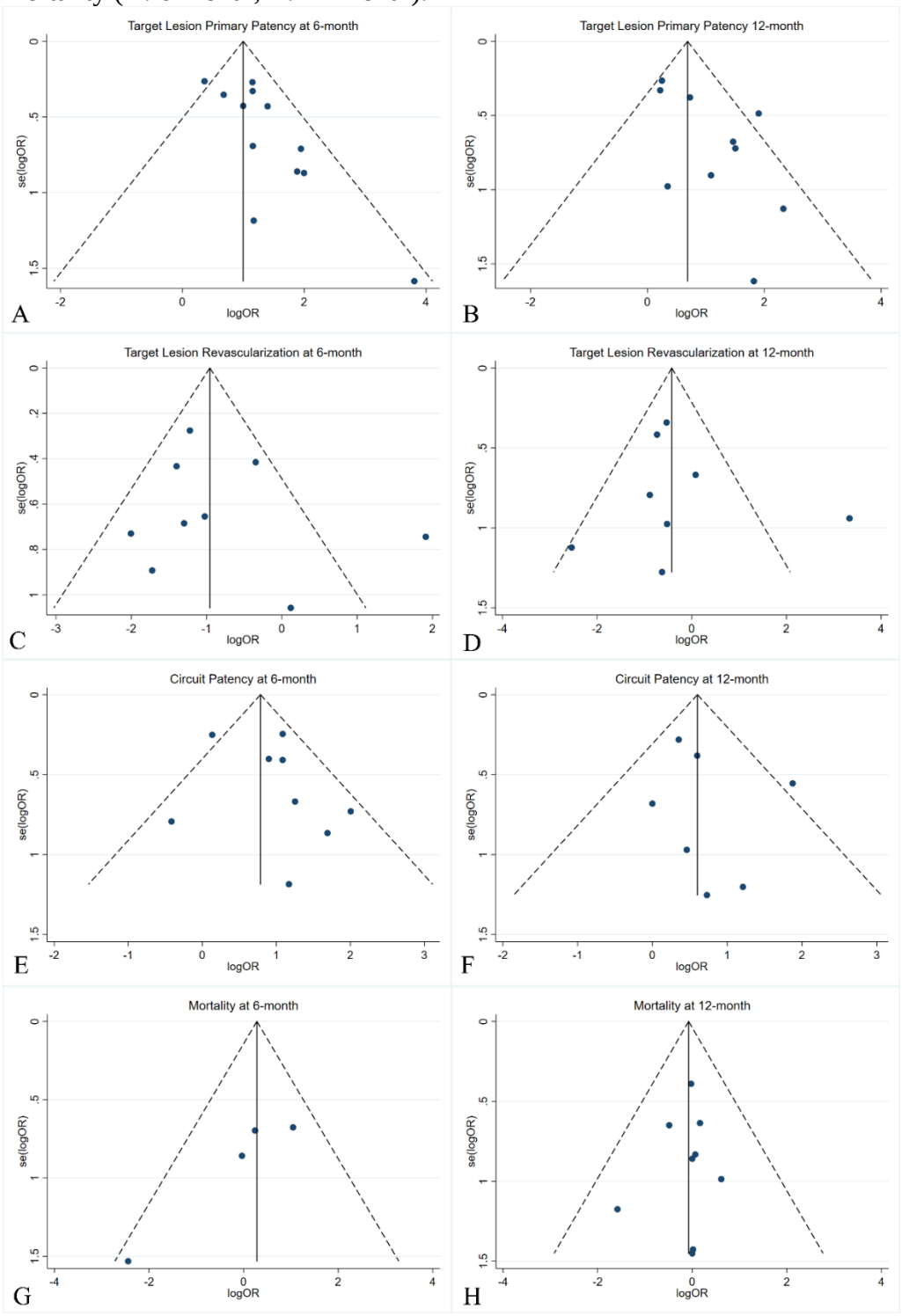

Figure S2: A) Sensitivity analysis of target lesion revascularization rate at 12-month. Individual odds ratio (OR) indicates the pooled outcome after removing one study at a time. B) target-lesion revascularization rate (TLRR) at 12-month excluding the study performed by Bjorkman et al. DCB: drug-coated balloon angioplasty. PBA: plain balloon angioplasty.

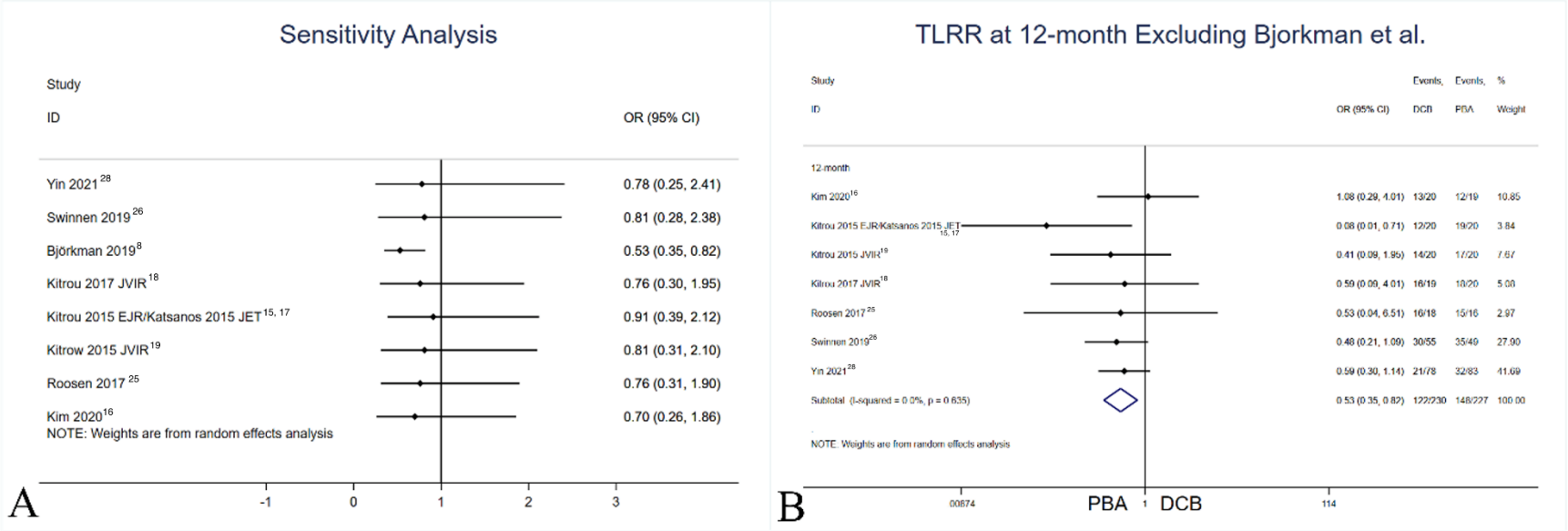

Figure S3. **Target lesion revascularization rate at 6-month and 12-month after removing Bjorkman et al.** DCB: drug-coated balloon angioplasty. PBA: plain balloon angioplasty.

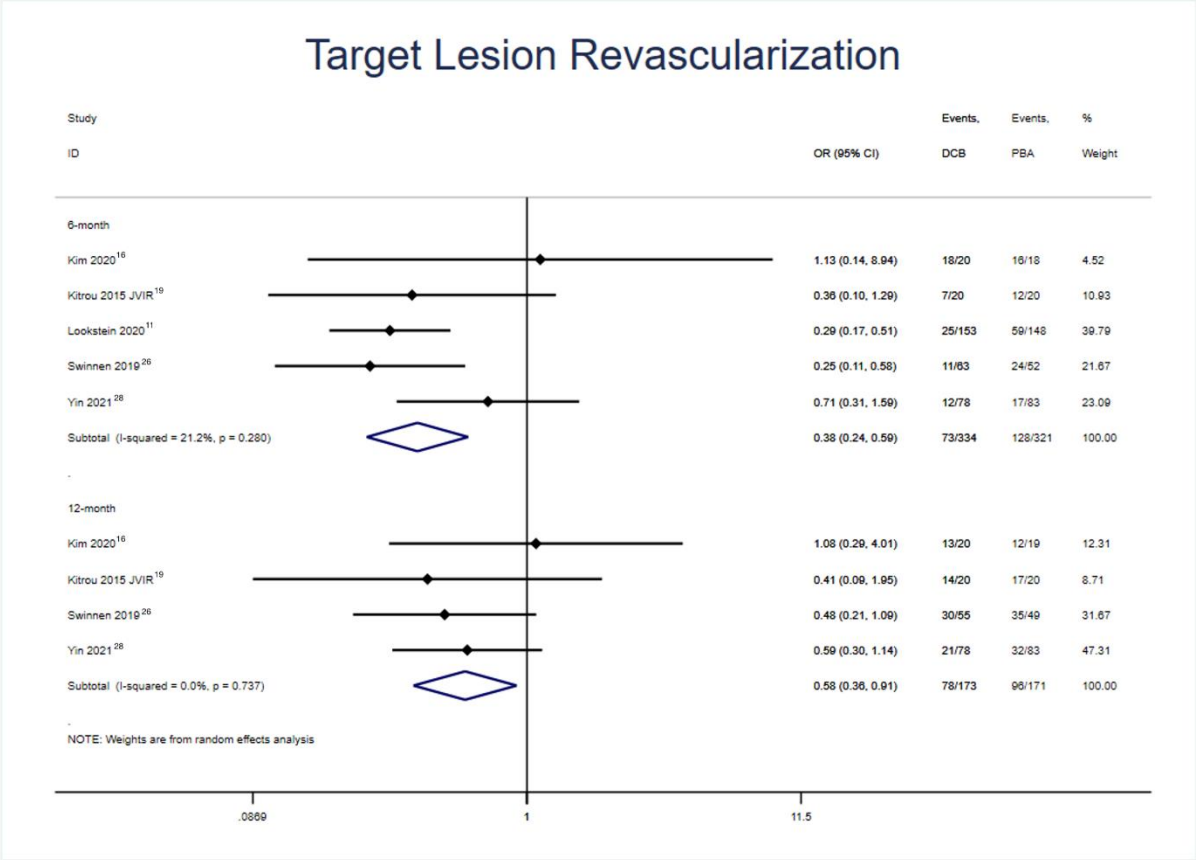

Figure S4. **Outcomes beyond 1-year follow-up**. CP: circuit patency. TLPP: target lesion primary patency. TLR: target lesion revascularization.